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Drug Degradation Prediction, In Silico Toxicity Assessment and Development of Stability-Indicating, Quality by Design Enabled UFLC Method for Sacubitril-Valsartan

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Abstract—Stability and impurity profiling of drugs is crucial in fixed-dose drug combinations as safety, efficacy, and purity depend on an individual drug's stability behaviour. The formation of drug degradants is lean-on various factors and the probabilities of drug degradation may increase in fixed-dose drug combination formulations. Additionally, drug impurity profiling can be studied with the aid of degradation prediction. In this context, a preliminary attempt was made to use Zeneth software to anticipate the degradation of combination medications. Due to the presence of mutagenic/carcinogenic impurities i.e. NDMA/NDEA in various batches of Valsartan, FDA announces a recall in the last few years. Therefore, Zeneth predictions were performed to explore the effect of the presence of mutagenic impurity (NDMA/NDEA) on the stability of drug. The toxicity of each predicted degradant was evaluated with the help of TEST, ProTox II and Lazar toxicity prediction tools. In the present work, the stability behavior of combination drugs was evaluated with the newly developed QbD enabled UFLC method. Sacubitril and Valsartan were subjected to various stress degradation conditions like acid, base, oxidative, thermal, and photo stress environment alone and in fixed-dose combinations to assess the stability.

Keywords: quality by design, sacubitril, stability indicating method, valsartan, zeneth

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INTRODUCTION

Sacubitril (SCB) is an angiotensin receptor-neprilysin inhibitor, and it is a first-in-class drug. SCB is a prodrug, but after de-ethylation, via esterases, it transformed to its active form as sacubitrilat. This activated form inhibits the enzyme neprilysin, as this enzyme degrades atrial and brain natriuretic peptides. These peptides are responsible for lowering of blood pressure via reducing blood volume [1, 2]. An angiotensin-receptor blocker, Valsartan (VLS), is used to manage hypertension and heart failure. It is an angiotensin receptor blocker, and it has 10000–30000-fold greater affinity for type 1 (AT 1) compared to type 2 (AT 2) receptors [2, 3].

SCB-VLS fixed-dose combination was approved in 2015 by the US and European Union, for the management of heart failure and decreased left ventricular ejection fraction. In India, the fixed-dose formulation of SCB-VLS was approved in July 2016 by CDSCO. During the trial, the combination was known as LCZ696 and it is highly indorsed for the replacement of ACE inhibitor. SCB-VLS accepted as a new therapeutic option for patients undergone systolic failure. Moreover, it is called as an Angiotensin Receptor Neprilysin inhibitor (ARNi) [1, 4, 5]. The chemical structures of SCB and VLS are depicted in Fig. 1.

Drug substance or drug products stability refers to the ability of a pharmaceuticals to maintain its identity, purity, strength, and quality over the course of retesting or shelf-life. Stress studies have been conducted in order to predict the stability of drug substance or drug product. Various regularity agencies were published the stability guidelines for the approval of drug products [6–9]. A stability study is essential to discriminate drug substances and their product's safety, efficacy, and stability. Furthermore, it provides evidences on the quality that changes over time

Abbreviations: ACN, Acetonitrile; CDSCO, Central Drugs Standard Control Organisation; FDA, Food and Drug Administration; MeOH, Methanol; NDEA, *N*-nitrosodiethylamine; NDMA, *N*-nitrosodimethylamine; QbD, Quality by Design; PDA, Photodiode-Array; SCB, Sacubitril; TEST, Toxicity Estimation Software Tool; UFLC, Ultra-Fast Liquid Chromatography; VLS, Valsartan.

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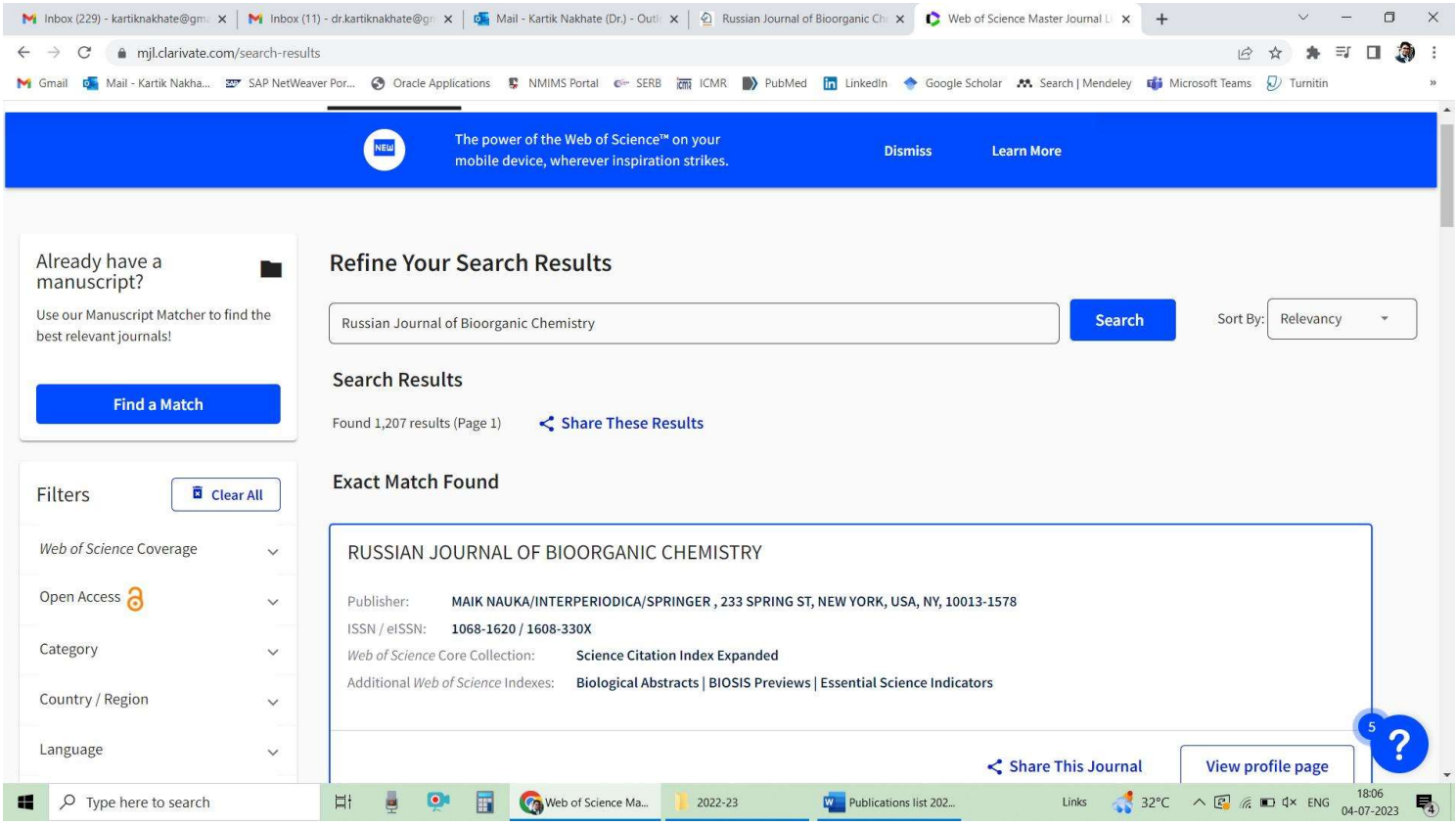
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